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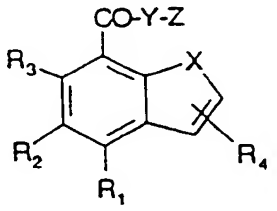

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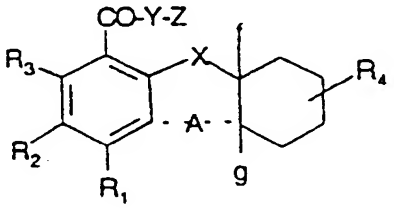

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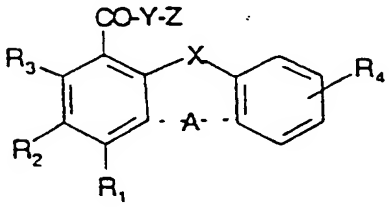

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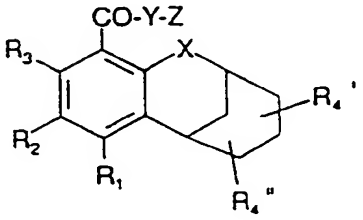

(I-4)

(57) Abstract

Compounds of formula (I), wherein formula (I) consists of formulae (I-1) to (I-4), and pharmaceutically acceptable salts thereof, and the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof, (I-1), (I-2), (I-3), (I-4) and their use as pharmaceuticals in the treatment of gastrointestinal disorders, cardiovascular disorders and CNS disorders. The compounds are 5-HT_4 receptor antagonists.

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HETEROCYCLIC CONDENSED BENZOIC ACID DERIVATIVES AS 5-HT4 RECEPTOR ANTAGONISTS

This invention relates to novel compounds having pharmacological activity, to a process for their preparation and to their use as pharmaceuticals.

European Journal of Pharmacology 146 (1988), 187-188, and Naunyn-Schmiedeberg's Arch. Pharmacol. (1989) 340:403-410, describe a non classical 5-hydroxytryptamine receptor, now designated the 5-HT_4 receptor, and that ICS 205-930, which is also a 5-HT_3 receptor antagonist, acts as an antagonist at this receptor. WO 91/16045 (SmithKline and French Laboratories Limited) describes the use of cardiac 5-HT_4 receptor antagonists in the treatment of atrial arrhythmias and stroke.

EP-A-501322 (Glaxo Group Limited) describes indole derivatives having 5-HT_4 antagonist activity.

WO 93/02677, WO 93/03725, WO 93/05038, WO 93/05040 and PCT/GB93/00506 (SmithKline Beecham plc) describe compounds having 5-HT_4 receptor antagonist activity.

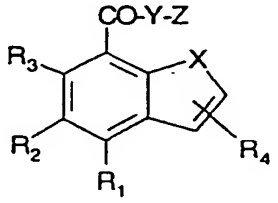
EP-A-234872 (Adria Laboratories Inc.) and EP-A-493041 (Erabomont Inc.), describe benzobicyclic carboxamides. EP-A-339950 (Rorer International Overseas Inc.) describes dibenzofurancarboxamides as 5-HT_3 receptor antagonists.

WO 92/09284 describes a process for preparing multicyclic oxy-containing ring system compounds as 5-HT_3 receptor antagonists.

It has now been discovered that certain novel compounds also have 5-HT_4 receptor antagonist properties.

When used herein, 'treatment' includes prophylaxis as appropriate.

Accordingly, the present invention provides compounds of formula (I), wherein formula (I) consists of formulae (I-1) to (I-4), and pharmaceutically acceptable salts thereof, and the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



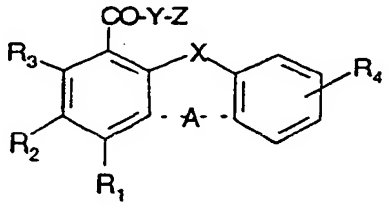
(I-1)

wherein

X is O or S;

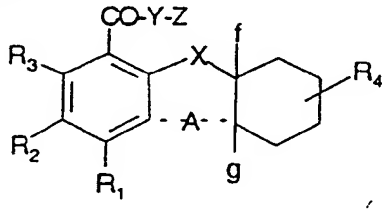
R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;
R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;
R_4 is hydrogen or C_{1-6} alkyl;



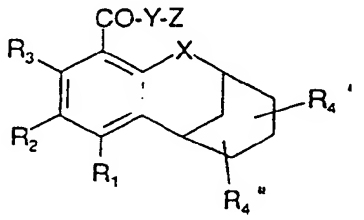
(I-2)

wherein
X is O or S;
A represents a single bond, $-CH_2-$, or CO or A is $(CH_2)_a$-E-$(CH_2)_b$ where one of a and b is 0 and the other is 0 or 1 and E is O, S or NH;
R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;
R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;
R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;
R_4 is hydrogen or C_{1-6} alkyl;



(I-3)

wherein
X is O or S;
A represents a single bond, $-CH_2-$, or CO or A is $(CH_2)_a$-E-$(CH_2)_b$ where one of a and b is 0 and the other is 0 or 1 and E is O, S or NH;
f and g are both hydrogen or together are a bond;
R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;
R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;
R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;
R_4 is hydrogen or C_{1-6} alkyl;



(I-4)

wherein

X is O or S;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;

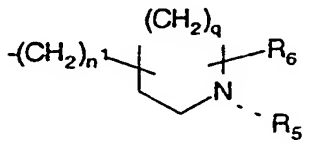
R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

R_4' and R_4'' are independently hydrogen or C_{1-6} alkyl;

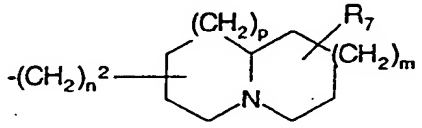
In formulae (I-1) to (I-4) inclusive:

Y is O or NH;

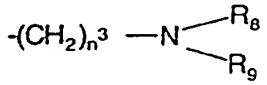
Z is of sub-formula (a), (b) or (c):



(a)



(b)



(c)

wherein

n^1 is 0, 1, 2, 3 or 4; n^2 is 0, 1, 2, 3 or 4; n^3 is 2, 3, 4 or 5;

q is 0, 1, 2 or 3; p is 0, 1 or 2; m is 0, 1 or 2;

R_5 is hydrogen, C_{1-12} alkyl, aralkyl or R_5 is $(CH_2)_z$-R_{10} wherein z is 2 or 3 and R_{10} is selected from cyano, hydroxyl, C_{1-6} alkoxy, phenoxy, $C(O)C_{1-6}$ alkyl, COC_6H_5, $-CONR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$ or $NR_{11}SO_2R_{12}$ wherein R_{11} and R_{12} are hydrogen or C_{1-6} alkyl; and

R_6, R_7 and R_8 are independently hydrogen or C_{1-6} alkyl; and

R_9 is hydrogen or C_{1-10} alkyl;

or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere;

in the manufacture of a medicament having 5-HT_4 receptor antagonist activity.

Examples of alkyl or alkyl containing groups include C_1, C_2, C_3, C_4, C_5, C_6, C_7, C_8, C_9, C_{10}, C_{11} or C_{12} branched, straight chained or cyclic alkyl, as appropriate. C_{1-4} alkyl groups include methyl, ethyl, *n*- and *iso*-propyl, *n*-, *iso*-, *sec*- and *tert*-butyl. Cyclic alkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl and cyclooctyl.

Aryl includes phenyl and naphthyl optionally substituted by one or more substituents selected from halo, C_{1-6} alkyl and C_{1-6} alkoxy.

Halo includes fluoro, chloro, bromo and iodo.

In formula (I-1):

R_1 is preferably hydrogen or amino.
R_2 is preferably hydrogen or halo.
R_3 is preferably hydrogen or halo.
R_4 is often hydrogen.

In formula (I-2):

R_1 is preferably hydrogen or amino.
R_2 is preferably hydrogen or halo.
R_3 is preferably hydrogen or halo.
R_4 is often hydrogen.

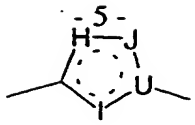
In formula (I-3):

R_1 is preferably hydrogen or amino.
R_2 is preferably hydrogen or halo.
R_3 is preferably hydrogen or halo.
R_4 is often hydrogen.

In formula (I-4):

R_1 is preferably hydrogen or amino.
R_2 is preferably hydrogen or halo.
R_3 is preferably hydrogen or halo.
R_4' and R_4'' are often hydrogen.

A suitable bioisostere for the amide or ester linkage containing Y in formula (I), is of formula (d):



(d)

wherein

the dotted circle represents one or two double bonds in any position in the 5-membered ring; H, J and I independently represent oxygen, sulphur, nitrogen or carbon, provided that at least one of H, J and I is other than carbon; U represents nitrogen or carbon.

Suitable examples of (d) are as described for X, Y and Z in EP-A-328200 (Merck Sharp & Dohme Ltd.), such as an oxadiazole moiety.

Y is preferably O or NH.

When Z is of sub-formula (a), n^1 is preferably 2, 3 or 4 when the azacycle is attached at the nitrogen atom and n^1 is preferably 1 when the azacycle is attached at a carbon atom, such as the 4-position when q is 2.

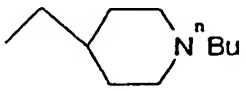
When Z is of sub-formula (b), n^2 is preferably such that the number of carbon atoms between the ester or amide linkage is from 2 to 4 carbon atoms.

Suitable values for p and m include p = m = 1; p = 0, m = 1, p = 1, m = 2, p = 2, m = 1.

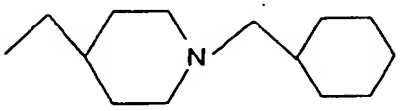
When Z is of sub-formula (c), n^3 is preferably 2, 3 or 4.

R_8 and R_9 are preferably both alkyl, especially one of R_8 and R_9 is C_4 or larger alkyl.

Specific values of Z of particular interest are as follows:



(i)



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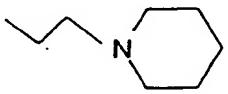

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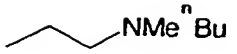

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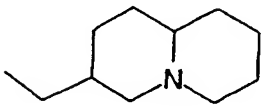

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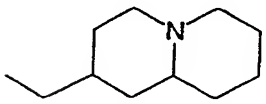

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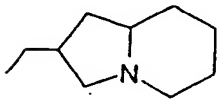


(vii)

The invention also provides novel compounds within formula (I) with side chains (i), (ii), (iii), (iv), (v), (vi) or (vii). In a further aspect, the piperidine ring in (i), (ii) or (iii) may be replaced by pyrrolidinyl or azetidinyl, and/or the N-substituent in (i) or (ii) may be replaced by C_3 or larger alkyl or optionally substituted benzyl.

In an alternative aspect, the N-substituent in formula (i) or (ii) may be replaced by $(CH_2)_nR^4$ as defined in formula (I) and in relation to the specific examples of EP-A-501322.

The pharmaceutically acceptable salts of the compounds of the formula (I) include acid addition salts with conventional acids such as hydrochloric, hydrobromic, boric, phosphoric, sulphuric acids and pharmaceutically acceptable organic acids such as acetic, tartaric, maleic, citric, succinic, benzoic, ascorbic, methanesulphonic, α-keto glutaric, α-glycerophosphoric, and glucose-1-phosphoric acids.

Examples of pharmaceutically acceptable salts include quaternary derivatives of the compounds of formula (I) such as the compounds quaternised by compounds R_x-T wherein R_x is C_{1-6} alkyl, phenyl-C_{1-6} alkyl or C_{5-7} cycloalkyl, and T is a radical corresponding to an anion of an acid. Suitable examples of R_x include methyl, ethyl and *n*- and *iso*-propyl; and benzyl and phenethyl. Suitable examples of T include halide such as chloride, bromide and iodide.

Examples of pharmaceutically acceptable salts also include internal salts such as N-oxides.

The compounds of the formula (I), their pharmaceutically acceptable salts, (including quaternary derivatives and N-oxides) may also form pharmaceutically acceptable solvates, such as hydrates, which are included wherever a compound of formula (I) or a salt thereof is herein referred to.

The compounds of formula (I) wherein CO-Y is an ester or amide linkage are prepared by conventional coupling of the Z moiety with the appropriate acid. Suitable methods are as described in GB 2125398A (Sandoz Limited), GB 1593146A, EP-A-36269, EP-A-289170 and WO 92/05174 (Beecham Group p.l.c.). When CO-Y is replaced by a heterocyclic bioisostere, suitable methods are described in EP-A-328200 (Merck Sharp & Dohme Limited). Reference is also made to EP-A-501322 (Glaxo Group Limited).

The invention also comprises a process for preparing the novel compounds of formula (I) which comprises reacting an appropriate acid derivative with an appropriate alcohol or amine. A process comprises reacting an acid derivative wherein the aromatic substituents are as required in the end compound of formula (I), or substituents convertible thereto, with an alcohol or amine containing Z or a group convertible thereto, and thereafter if necessary, converting the benzoic acid substituents and/or Z, and optionally forming a pharmaceutically acceptable salt.

Suitable examples of conversions in the aromatic substituents include chlorination of hydrogen to chloro, reduction of nitro to amino, dehydrohalogenation such as debromination. Any elaboration is, however, usually carried out prior to ester or amide coupling.

Suitable examples of conversions in the Z containing moiety include conventional modifications of the N-substituent by substitution and/or deprotection or, in the case of a 2-, 3- or 4- substituted piperidinyl desired end compound, reduction of an appropriate pyridyl derivative.

The compounds of the present invention are 5-HT_4 receptor antagonists and it is thus believed may generally be used in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

They are of potential interest in the treatment of irritable bowel syndrome (IBS), in particular the diarrhoea aspects of IBS, i.e., these compounds block the ability of 5-HT to stimulate gut motility via activation of enteric neurones. In animal models of IBS, this can be conveniently measured as a reduction of the rate of defaecation. They are also of potential use in the treatment of urinary incontinence which is often associated with IBS.

They may also be of potential use in other gastrointestinal disorders, such as those associated with upper gut motility, and as antiemetics. In particular, they are of potential use in the treatment of the nausea and gastric symptoms of gastro-

oesophageal reflux disease and dyspepsia. Antiemetic activity is determined in known animal models of cytotoxic-agent/radiation induced emesis.

Specific cardiac 5-HT_4 receptor antagonists which prevent atrial fibrillation and other atrial arrhythmias associated with 5-HT, would also be expected to reduce occurrence of stroke (see A.J. Kaumann 1990, Naumyn-Schmiedeberg's Arch. Pharmacol. 342, 619-622, for appropriate animal test method).

Anxiolytic activity is likely to be effected via the hippocampus (Dumuis *et al* 1988, Mol Pharmacol., 34, 880-887). Activity can be demonstrated in standard animal models, the social interaction test and the X-maze test.

Migraine sufferers often undergo situations of anxiety and emotional stress that precede the appearance of headache (Sachs, 1985, Migraine, Pan Books, London). It has also been observed that during and within 48 hours of a migraine attack, cyclic AMP levels are considerably increased in the cerebrospinal fluid (Welch *et al.*, 1976, Headache 16, 160-167). It is believed that a migraine, including the prodomal phase and the associated increased levels of cyclic AMP are related to stimulation of 5-HT_4 receptors, and hence that administration of a 5-HT_4 antagonist is of potential benefit in relieving a migraine attack.

Other CNS disorders of interest include schizophrenia, Parkinson's disease and Huntingdon's chorea.

The invention also provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

Such compositions are prepared by admixture and are usually adapted for enteral such as oral, nasal or rectal, or parenteral administration, and as such may be in the form of tablets, capsules, oral liquid preparations, powders, granules, lozenges, reconstitutable powders, nasal sprays, suppositories, injectable and infusable solutions or suspensions. Orally administrable compositions are preferred, since they are more convenient for general use.

Tablets and capsules for oral administration are usually presented in a unit dose, and contain conventional excipients such as binding agents, fillers, diluents, tabletting agents, lubricants, disintegrants, colourants, flavourings, and wetting agents. The tablets may be coated according to well known methods in the art, for example with an enteric coating.

Suitable fillers for use include cellulose, mannitol, lactose and other similar agents. Suitable disintegrants include starch, polyvinylpolypyrrolidone and starch derivatives such as sodium starch glycollate. Suitable lubricants include, for example, magnesium stearate.

Suitable pharmaceutically acceptable wetting agents include sodium lauryl sulphate. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters such as esters of glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and if desired conventional flavouring or colouring agents.

Oral liquid preparations are usually in the form of aqueous or oily suspensions, solutions, emulsions, syrups, or elixirs or are presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, emulsifying agents, non-aqueous vehicles (which may include edible oils), preservatives, and flavouring or colouring agents.

The oral compositions may be prepared by conventional methods of blending, filling or tabletting. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. Such operations are, of course, conventional in the art.

For parenteral administration, fluid unit dose forms are prepared containing a compound of the present invention and a sterile vehicle. The compound, depending on the vehicle and the concentration, can be either suspended or dissolved. Parenteral solutions are normally prepared by dissolving the compound in a vehicle and filter sterilising before filling into a suitable vial or ampoule and sealing. Advantageously, adjuvants such as a local anaesthetic, preservatives and buffering agents are also dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum.

Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilised by exposure of ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound of the invention.

The invention further provides a method of treatment or prophylaxis of irritable bowel syndrome, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine in mammals, such as humans, which comprises the administration of an effective amount of a compound of the formula (I) or a pharmaceutically acceptable salt thereof.

An amount effective to treat the disorders hereinbefore described depends on the relative efficacies of the compounds of the invention, the nature and severity of the disorder being treated and the weight of the mammal. However, a unit dose for a 70kg adult will normally contain 0.05 to 1000mg for example 0.5 to 500mg, of the compound of the invention. Unit doses may be administered once or more than once a day, for example, 2, 3 or 4 times a day, more usually 1 to 3 times a day, that is in the range of approximately 0.0001 to 50mg/kg/day, more usually 0.0002 to 25 mg/kg/day.

No adverse toxicological effects are indicated within the aforementioned dosage ranges.

The invention also provides a compound of formula (I) or a pharmaceutically acceptable salt thereof for use as an active therapeutic substance, in particular for use in the treatment of irritable bowel syndrome, gastro-oesophageal reflux disease, dyspepsia, atrial arrhythmias and stroke, anxiety and/or migraine.

The following Examples illustrates the preparation of compounds of formula (I), and the following Descriptions relate to the preparation of intermediates. The compounds of formula (I-1) and intermediates are prepared in Examples and Descriptions 1-1, 2-1 etc, the compounds of formula (I-2) are prepared in Examples and Descriptions 1-2, 2-2 etc and similarly for the compounds of formulae (I-3) to (I-4).

It will be appreciated that any compound prepared wherein Y is O may be provided as the corresponding compound wherein Y is NH.

A preferred compound corresponds to any of the compounds prepared in the Examples, but wherein there is an amino substituent in the 4-position and a chloro substituent in the 5-position of the benzoic acid nucleus depicted in formulae (I-1) to (I-4) inclusive.

Description 1-1 (intermediate for Example 1-1)

a) **Methyl-4-acetylamino-3-allyl-5-chloro-2-hydroxybenzoate**

A mixture of methyl 4-acetylamino-5-chloro salicylate (EP-A-0339950), (17.0g, 0.070 mol), allylbromide (6.32 ml, 0.073 mol), acetone (350 ml) and potassium carbonate (19.35g, 0.140 mol) was heated to reflux with stirring. After 23h, the reaction mixture was allowed to cool, was filtered, and the filtrate evaporated under reduced pressure and dried *in vacuo* to give a pale brown solid. The solid was redissolved in 1,2-dichlorobenzene (300 ml) and was heated to reflux with stirring. After 24h the reaction mixture was allowed to cool, and was evaporated under reduced pressure. The resultant semi-solid brown residue was then purified by silica gel chromatography (2:1 Pentane: EtOAc → EtOAc as eluant) to give the ***title compound*** (8.24g, 42%) as a yellow solid.

^{1}H NMR (200 MHz, $CDCl_3$) δ :

11.10 (s, 1H), 7.81 (s, 1H), 7.04 (s, 1H), 5.88 (m, 1H), 5.00 (m, 2H), 3.95 (s, 3H), 3.45 (d, 2H), 2.25 (s, 3H).

b) **Methyl-4-acetylamino-5-chloro-2-hydroxy-3-(2-oxoethyl) benzoate**

The product from a) (8.23g, 0.029 mol) was dissolved in acetone (300 ml) and water (60 ml), treated with N-methylmorpholine-N-oxide (6.79g, 0.058 mol), followed by 4% wt osmium tetroxide in water (1.82 ml, 0.0029 mol) and stirred at room temperature overnight. After 21 h, 10% sodium bisulphite solution (100 ml) was added, and the mixture was stirred for ½ h, before the acetone was evaporated under reduced pressure. The reaction mixture was then partitioned between EtOAc and water. The aqueous layer was then extracted with EtOAc (2X), and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give an off white solid, which was dried *in vacuo*. The solid was then redissolved in methanol (250 ml) and treated with a solution of sodium periodate (9.41g, 0.044 mol) in water (60 ml) with stirring. The mixture was then stirred at room temperature overnight, before the methanol was removed *in vacuo*. The residue was then partitioned between EtOAc and water. The aqueous layer was then extracted with EtOAc, and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a dark brown oil. The oil was then purified by the silica-gel chromatography (EtOAc as eluant) to give the ***title compound*** as a brown foam (5.90g, 71%)

^{1}H NMR (200 MHz, CD_3OD) δ :

8.00 (s, 1H), 4.92 (t, 1H), 4.10 (s, 3H), 3.12 (d, 2H), 2.33 (s, 3H)

c) 2-Acetoxy-7-carbomethoxy-5-chloro-4-diacetylamino-2,3-dihydrobenzofuran

The product from **b)** (5.90g, 0.021 mol) was dissolved in a mixture of acetic anhydride (55 ml) and pyridine (55 ml), a few crystals of 4-dimethylaminopyridine were added, and the mixture was stirred at room temperature overnight. After 20h, the reaction mixture was partitioned between EtOAc and water. The aqueous layer was then extracted with EtOAc, and the combined organic layers were dried (Na_2SO_4), and evaporated under reduced pressure to give a brown oil, which was dried *in vacuo*. The oil was then purified by silica-gel chromatography (2:1 Pentane:EtOAc as eluant) to give the ***title compound*** as a pale brown oil. (2.87g, 37%)

^1H NMR (250 MHz, $CDCl_3$), δ :

8.00 (s, 1H), 7.00 (dd, 1H), 3.92 (s, 3H), 3.38 (dd, 1H), 3.00 (dd, 1H), 2.32 (s, 3H), 2.28 (s, 3H), 2.10 (s, 3H).

d) 7-Carbomethoxy-5-chloro-4-diacetylaminobenzo[b]furan

The product from **c)** (2.87g, 7.77 mmol) was dissolved in trifluoroacetic acid (50 ml) and heated to reflux with stirring. After 1h, the reaction mixture was allowed to cool and was evaporated under reduced pressure. The residue was partitioned between aq. $NaHCO_3$ and dichloromethane. The aqueous layer was then extracted with dichloromethane (2x), and the combined organic layers were dried (Na_2SO_4), and evaporated under reduced pressure to give a brown oil, which was purified by silica-gel chromatography (1:1 Petrol: diethylether as eluant) to give the ***title compound*** as a pale yellow oil (0.765g, 32%).

^1H NMR (250 MHz, $CDCl_3$), δ :

8.10 (s, 1H), 7.81 (d, 1H), 6.70 (d, 1H), 4.10 (s, 3H), 2.30 (s. 6H).

Description 2-1 (intermediate for Example 2-1)

a) (2-Carboxyphenylthio) Acetic Acid

A solution of thiosalicylic acid (10.0g; 64.9 mmol) in H_2O (200 ml) containing sodium carbonate (34.5g; 0.32 mol) was treated with sodium chloroacetate (7.56g; 64.9 mmol) in H_2O (100 ml). The whole was heated at reflux (2 hours), cooled and acidified to pH2 with c.HCl. The material that crystallised was collected by filtration and dried *in vacuo* to yield the ***title compound*** as an orange powder (12.5g; 91%)

^1H NMR (250MHz; CD_3SOCD_3) δ :

13.10 - 12.85 (bs, 2H), 7.90 (d, 1H), 7.50 (t, 1H), 7.35 (d, 1H), 7.20 (t, 1H), 3.80 (s, 2H)

b) **Thioindoxyl-7-carboxylic Acid**

(2-Carboxyphenylthio)acetic acid (6.5g; 30.66 mmol) was heated at reflux in thionyl chloride (45 ml) for 1 hour, cooled, evaporated *in vacuo* and the residue azeotroped with toluene. The residue was redissolved in 1,2-dichlorobenzene (8.0 ml) and treated with aluminium chloride (8.18g; 61.3 mmol) portionwise. The whole was heated to 45-50° C (1 hour) then treated with ice and sodium hydroxide until the mixture was basic. The aqueous layer was separated, extracted with diethyl ether and then acidified with cHCl to pH1 and left to stand. The precipitate that formed was collected by filtration and dried *in vacuo* to yield the ***title compound*** as a red powder (2.45g; 41%)

^{1}H NMR (250MHz; CD_3SOCD_3) δ :

8.05-7.95 (m, 2H), 7.50 (t, 1H), 6.55 (s, 1H)

c) **Benzothiophene-7-carboxylic Acid**

A solution of thioindoxyl-7-carboxylic acid (0.3g; 1.55 mmol) in glacial acetic acid (5ml) was treated with zinc amalgam (made from zinc dust (1.14g) and the whole heated at reflux (18h), cooled, filtered through kieselguhr and the filtrate evaporated *in vacuo* to yield the ***title compound*** and 2,3-dihydrobenzothiophene-7-carboxylic acid (1:1) as a red solid (0.152g; 55%).

^{1}H NMR (250 MHz, CD_3SOCD_3) δ :

8.15 (d, 1H), 8.05 (d, 1H), 7.85 (d, 1H), 7.50 (t, 2H)

Example 1-1 [$R_1 = NH_2$, $R_2 = Cl$, $R_3 = H$, $R_4 = H$, X = O, Y = NH, Z = (i)]
(1-Butyl-4-piperidinylmethyl)-4-amino-5-chloro-benzo[b]furan-7-carboxamide

The product from Description 1 (0.765g, 2.47mmol) was dissolved in a mixture of 10% sodium hydroxide (15 ml) and ethanol (15 ml). The reaction mixture was then heated to reflux. After 23 h, the reaction mixture was allowed to cool. The ethanol was then removed by evaporation under reduced pressure and the aqueous residue acidified to pH2 using c. HCl. The resulting grey solid was then filtered off and dried *in vacuo*. The solid was then suspended in a mixture of acetonitrile (10 ml) and DMF (10 ml) and was treated with 1,1,carbonyldiimidazole (0.440g, 2.71 mmol) with stirring. After 20h, the reaction mixture was evaporated under reduced pressure and dried *in vacuo*. The crude imidazolide was then suspended in dry THF (20 ml) and N-butyl-4-piperidinylmethylamine (0.461g, 2.71 mmol) (W093/05038) in dry THF (5 ml) was added. The mixture was then heated to reflux under argon. After 4 h, the reaction mixture was allowed to cool and was evaporated under reduced pressure. The residue was partitioned between EtOAc and 10% NaOH. The aqueous layer was then extracted with EtOAc, and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a brown solid, which was

purified by silica-gel chromatography (20% MeOH/EtOAc as eluant) to give the ***title compound*** as a white foam (0.425g, 46%)
m.pt 88-89° C (from CH_2Cl_2/60-80 petrol)
^1H NMR (200MHz, $CDCl_3$), δ:
8.04 (s, 1H), 7.64 (d, 1H),7.35 (brt, 1H), 6.81 (d, 1H), 4.71 (s, 2H), 3.43 (t, 2H), 2.97 (d, 2H), 2.33 (t, 3H), 2.05 - 1.60 (m, 5H), 1.55 - 1.20 (m, 5H), 0.91 (t, 3H).

Example 2-1 [R_1 = H, R_2 = H, R_3 = H, R_4 = H, X = S, Y = O, Z = (i)]
(1-Butyl-4-piperidinylmethyl)benzothiophene-7-carboxylate

A 1:1 mixture of benzothiophene-7-carboxylic acid and 2,3-dihydrobenzothiophene-7-carboxylic acid (0.262g; 1.46 mmol) was dissolved in dry DMF (5ml) and treated with 1,1-carbonyldiimidazole (0.161g; 1.61 mmol). The mixture was stirred (72 hours). N-butyl-4-piperidinylmethanol (WO 93/05038) (0.275g; 1.61 mmol) was dissolved in dry THF (10 ml) under Ar and treated with methyllithium (1.18 ml of a 1.5M solution in Et_2O; 1.77 mmol) then stirred for 15 minutes. This was treated with the solution of imidazolides and the whole stirred (72 hours). Evaporated *in vacuo* and partitioned H_2O/EtOAc. The organic layer was separated, dried over Na_2SO_4 and filtered, then the filtrate evaporated *in vacuo* to an orange oil. The oil was purified by flash silica-gel chromatography and eluted with $CHCl_3$ → 3% MeOH/$CHCl_3$ to yield a brown oil which was purified by HPLC separation to y ield the ***title compound*** as a clear gum (0.009g; 2%).
^1H NMR (250 MHz; $CDCl_3$) δ:
8.15 (d, 1H), 8.05 (d, 1H), 7.60 (d, 1H), 7.30 (d, 1H), 7.05 (t, 1H), 4.30 (d, 2H), 3.05-2.95 (m, 2H), 2.35 (t, 2H), 2.00-1.75 (m, 5H), 1.60-1.25 (m, 6H), 0.90 (t, 3H).

Example 3-1 [R_1 = H, R_2 = Cl, R_3 = H, R_4 = H, X = O, Y = O, Z = (i)]
(1-Butyl-4-piperidinylmethyl)-5-chlorobenzo[b]furan-7-carboxylate

5-Chlorobenzo[b]furan-7-carboxylic acid [US patent 4888353; 33f] (0.5g; 2.54 mmol) was suspended in thionyl chloride (20 ml) and heated at reflux (30 minutes) until clear. The solution was evaporated *in vacuo* and the residue redissolved in dry THF (10 ml). N-butyl-4-piperidinylmethanol (WO 93/05038) (0.479g; 2.80 mmol) was dissolved in dry THF (5 ml) under Ar and treated with methyllithium (2.05 ml of a 1.5M solution in diethyl ether; 3.08 mmol). The mixture was stirred at (15 minutes) and treated with the acid chloride solution dropwise. The solution was stirred (18 hours) evaporated *in vacuo* and the residue purified by flash silica gel chromatography with $CHCl_3$ → 5% EtOH/$CHCl_3$ as eluant to yield a pale yellow oil/solid. This material was triturated with pentane, cooled to -78° C and the solid that formed collected by filtration and dried *in vacuo* to yield the ***title***

compound as a pale yellow solid (0.11g; 13%), mp = 39-40° C.
^{1}H NMR ($CDCl_3$, 250 MHz) δ :
7.90 (d, 1H), 7.80 (dd, 2H), 6.80 (d, 1H), 4.30 (d, 2H), 3.05 (d, 2H), 2.40 (t, 2H), 2.10-1.80 (m, 5H), 1.65-1.25 (m, 6H), 0.95 (t, 3H)

Example 4-1 [R_1 = H, R_2 = Cl, R_3 = H, R_4 = H, X = O, Y = NH, Z = (i)]
(1-Butyl-4-piperidinylmethyl)-5-chlorobenzo[b]furan-7-carboxamide
5-chlorobenzo[b]furan-7-carboxylic acid [US patent 4888353; 33f] (0.18g; 0.92 mmol) was suspended in thionyl chloride (2 ml) and heated at reflux (30 minutes) until clear. The mixture was cooled, evaporated *in vacuo* and the residue azeotroped with toluene. The residue was redissolved in dry THF (4 ml) and treated with triethylamine (0.13 ml; 0.92 mmol) and N-butyl-4-piperidinylmethylamine (W093/05038) (0.171g; 1.01 mmol). The solution was stirred at RT (1 hour), evaporated *in vacuo* and partitioned $H_2O/CHCl_3$. The organic phase was dried over Na_2SO_4, filtered and evaporated *in vacuo* to a yellow oil. The oil was purified by flash silica-gel chromatography with $CHCl_3 \rightarrow$ 2% MeOH/$CHCl_3$ as eluant to yield the ***title compound*** as a pale yellow oil (0.3g; 94%), which was converted to the oxalate salt, mp = 109-110° C.
^{1}H NMR (250 MHz, $CDCl_3$) (free base) δ :
8.10 (d, 1H), 7.75 (d, 1H), 7.70 (d, 1H), 7.55 - 7.45 (m, 1H), 6.85 (d, 1H), 3.45 (t, 2H), 3.00 (d, 2H), 2.35 (t, 2H), 2.05 - 1.65 (m, 5H), 1.55 - 1.25 (m, 6H), 0.90 (t, 3H).

Description 1-2 (intermediate for Example 1-2)
Dibenzofuran-4-carboxylic acid

A solution of ^{n}BuLi (9.7 ml, 1.36 M in hexanes) in hexane (30 ml) was treated with N,N,N',N'-tetramethylethylenediamine (2.0 ml), followed by addition of dibenzofuran (2g). Stirring was continued at room temperature overnight. The mixture was poured onto solid CO_2 and diluted with water. The layers were separated, the aqueous layer acidified to pH2 with 5N HCl and extracted with dichloromethane. The organic phase was dried (Na_2SO_4), filtered and concentrated *in vacuo* to afford title compound as an off-white solid (1.60g).
^{1}H NMR 250 MHz (d_6-DMSO)
δ 13.34(bs,1H), 8.42(d,1H), 8.21(d,1H), 8.04(d,1H), 7.80(d,1H), 7.36-7.52(m,3H).

Example 1-2 [R_1 = H, R_2 = H, R_3 = H, R_4 = H, X = O, A is a single bond, Y = O, Z = (i)]

1-Butylpiperidin-4-ylmethyldibenzofuran-4-carboxylate hydrochloride

To a solution of dibenzofuran-4-carboxylic acid (1.00g) in acetonitrile (50 ml) was added 1,1-carbonyldimidazole (763 mg). Stirring was continued at room temperature for 2h. The solvent was concentrated *in vacuo* to afford crude imidazolide.

Methyllithium (3.13 ml, 1.5 M in diethyl ether) was added dropwise to a solution of 1-butyl-4-hydroxymethylpiperidine (808 mg) in dry THF (15 ml) at 0°C. Stirring was continued at 0°C under a nitrogen atmosphere for 30 min. A solution of crude imidazolide in dry THF (20 ml) was added to the reaction mixture and stirring continued at room temperature overnight. Water (2 ml) was added and the solvent concentrated *in vacuo*. The residue was partitioned between chloroform and water. The organic phase was dried (Na_2SO_4), filtered and concentrated under reduced pressure. The residue was chromatographed on silica using chloroform and ethanol as eluant to afford pure ester. Treatment with ethereal HCl gave the title compound as a solid (1.00g).

^{1}H NMR 250 MHz ($CDCl_3$) (Free base)

δ: 8.12((t,2H), 7.98(d,1H), 7.68(d,1H), 7.50(t,1H), 7.34-7.45(m,2H), 4.32(d,2H), 3.02(d,2H), 2.35(t,2H), 1.82-2.08(m,5H), 1.44-1.63(m,4H), 1.26-1.39(m,2H), 0.94(t,3H).

Example 2-2 [R_1 = H, R_2 = H, R_3 = H, R_4 = H, X = O, A is -CH_2-, Y = O, Z = (i)]

(1-Butyl-4-piperidinylmethyl)-9H-xanthene-4-carboxylate

The title compound is prepared from 9H-xanthene-4-carboxylic acid (P.Yates et al. , Can J. Chem., 1975, 53, 2045 and lithium (1-butylpiperidin-4-yl) methoxide via the imidazolide.

Example 3-2 [R_1 = H, R_2 = H, R_3 = H, R_4 = H, X = O, A is -CO-, Y = O, Z = (i)]

(1-Butyl-4-piperidinylmethyl)-9-oxo-9H-xanthene-4-carboxylate

The title compound is prepared from 9-oxo-9H-xanthene-4-carboxylic acid (S.Akagi et al.,J.Pharm. Soc. Jpn., 1954, 74, 610) (R.Anschutz et al., Ber., 1922, 55, 686) and lithium (1-butylpiperidin-4-yl) methoxide *via* the imidazolide

Example 4-2 [R_1 = H, R_2 = H, R_3 = H, R_4 = H, X = O, A is -NH-, Y = O, Z = (i)]

(1-Butyl-4-piperidinylmethyl)-10H-phenoxazine-4-carboxylate

The title compound is prepared from 10H -phenoxazine-4-carboxylic acid and lithium (1-butylpiperidin-4-yl) methoxide *via* the imidazolide

Example 5-2 [R_1 = H, R_2 = H, R_3 = H, R_4 = H, X = O, A is a single bond, Y = NH, Z = (i)]

(1-Butyl-4-piperidinylmethyl)-1-amino-2-chlorodibenzofuran-4-carboxamide

The ***title compound*** was prepared from 1-amino-2-chlorodibenzofuran-4-carboxylic acid (EP-A-0339950) according to the methodology described in Example 2-3, and was converted to its oxalate salt.

m.pt 177-178° C

^{1}H NMR (250 MHz, $CDCl_3$), (Free base) δ :

8.12 (s, 1H), 7.78 (d, 1H), 7.54 (d, 1H), 7.42 (m, 3H), 4.93 (s, 2H), 3.43 (t, 2H), 2.92 (d, 2H), 2.28 (t, 2H), 1.91-1.65 (m, 5H), 1.48-1.35 (m, 6H), 0.87 (t, 3H).

Example 6-2 [R_1 = H, R_2 = Cl, R_3 = NH_2, R_4 = H, X = O, A is a single bond, Y = O, Z = (i)]

(1-Butyl-4-piperidinylmethyl)-1-amino-2-chlorodibenzofuran-4-carboxylate

The ***title compound*** was prepared from 1-amino-2-chlorodibenzofuran-4-carboxylic acid (EP-A-0339950) according to the methodology described in Example 1-3 and was converted to its oxalate salt.

mpt. 199-200° C

^{1}H NMR (250 MHz, $CDCl_3$) (Free base) δ:

8.08 (s, 1H), 7.80 (d, 1H), 7.70 (d, 1H), 7.47 (m, 2H), 5.11 (s, 2H), 4.19 (d, 2H), 3.05 (bd, 2H), 2.39 (t, 2H), 2.12-1.80 (m, 5H), 1.54 (m, 4H), 1.32 (m, 2H), 0.94 (t, 3H).

Example 7-2 [R_1 = H, R_2 = Cl, R_3 = H, R_4 = H, X = O, A is a single bond, Y = O, Z = (i)]

(1-Butyl-4-piperidinylmethyl)-2-chlorodibenzofuran-4-carboxylate

The ***title compound*** was prepared from 2-chlorodibenzofuran-4-carboxylic acid (EP-A-0339950) according to the methodology described in Example 3-3.

mpt. 80-82° C

^{1}H NMR (250 MHz), $CDCl_3$ (Free base) δ :

8.12 (d, 1H), 8.05 (d, 1H), 7.92 (d, 1H), 7.68 (d, 1H), 7.53 (t, 1H), 7.40 (t, 1H), 4.32 (d, 1H), 3.03 (d, 2H), 2.38 (t, 2H), 2.10-1.82 (m, 5H), 1.55 (m, 4H), 1.32 (m, 2H), 0.90 (t, 3H).

Example 1-3 [R_1 = H, R_2 = H, R_3 = H, R_4 = H, X = O, A is a single bond, f, g = H, Y = O, Z = (i)]

(1-Butyl-4-piperidinylmethyl)-1-amino-2-chloro-5a,6,7,8,9,9a-tetrahydrodibenzofuran-4-carboxylate

1-Amino-2-chloro-5a,6,7,8,9,9a-hexahydrodibenzofuran-4-carboxylic acid (EP-A-0339950) (0.267g, 0.998 mmol) was suspended in acetonitrile and treated with bis-carbonyldiimidazole (0.178g, 1.098 mmol) with stirring. After 4 h, the reaction mixture was evaporated under reduced pressure and dried *in vacuo* to give the crude imidazolide as a white solid. Meanwhile, a solution of 1-butyl-4-piperidinemethanol (WO 93/103725) (0.171g, 0.998 mmol) in dry THF (8 ml) was treated with 1.5M methyllithium in Et_2O (0.665 ml, 0.998 mmol) with stirring under argon. After 0.25 h, a suspension of the crude imidazolide in dry THF (5 ml) was added slowly. After 24 h, the reaction mixture was evaporated under reduced pressure and partitioned between EtOAc and water. The aqueous layer was then extracted with EtOAc and the combined organic layers were dried (Na_2SO_4) and evaporated under reduced pressure to give a yellow oil, which was purified by silica-gel chromatography (5% MeOH/CH_2Cl_2 as eluant) to give the ***title compound*** as a pale yellow oil (0.082g, 20%), which was converted to its oxalate salt m.pt. 105-107°C.

^{1}H NMR (200 MHz, $CDCl_3$) (free base) δ:

7.68 (s, 1H), 4.70 (m, 1H), 4.35 (s, 2H), 4.12 (d, 2H), 3.13 (bd, 2H), 3.00 (m, 1H), 2.55-1.45 (m, 17H), 1.43-1.15 (m, 4H), 0.93 (t, 3H).

Example 2-3 [R_1 = H, R_2 = Cl, R_3 = NH_2, R_4 = H, X = O, A is a single bond, f, g, together are a bond, Y = NH, Z = (i)]

(1-Butyl-4-piperidinylmethyl)-1-amino-2-chloro-5a,6,7,8,9,9a-tetrahydrodibenzofuran-4-carboxamide

1-Amino-2-chloro-5a,6,7,8,9,9a-hexahydrodibenzofuran-4-carboxylic acid (EP-A-339950) (0.292g, 1.092 mmol) was suspended in acetonitrile (20 ml) and treated with bis-carbonyldiimidazole (0.186g, 1.46 mmol) with stirring. After 20h, the reaction mixture was evaporated under reduced pressure and dried *in vacuo* to give the crude imidazolide as a white solid. The imidazolide was then redissolved in dry THF (10 ml) and (1-butyl-4-piperidinyl) methylamine (WO 93/05038) (0.204 g, 1.201 mmol) in dry THF (2 ml) was added under Ar. The mixture was then heated under reflux. After 8 h, the reaction mixture was allowed to cool, and was evaporated under reduced pressure. The residue was then partitioned between CH_2Cl_2 and aq. $NaHCO_3$. The aqueous layer was then extracted with CH_2Cl_2 (1X), and the combined organic layers were dried (Na_2SO_4), and evaporated under reduced pressure to give a colourless oil, which was purified by chromatography (10%

$MeOH/CH_2Cl_2$ as eluant) to give the ***title compound*** as a colourless oil (0.161 g, 35%) that was converted to its oxalate salt.

m. pt 214-215° C

^1H NMR (250 MHz $CDCl_3$) (free base) δ :

7.82 (s, 1H), 7.54 (t, 1H), 4.72 (m, 1H), 4.29 (s, 2H), 3.32 (t, 2H), 3.03 (m, 3H), 2.32 (m, 3H), 2.12-1.15 (m, 18H), 0.91 (t, 3H)

Example 3-3 [R_1 = H, R_2 = Cl, R_3 = H, R_4 = H, X = O, A is a single bond, f, g = H, Y = O, Z = (i)]

(1-Butyl-4-piperidinylmethyl)-2-chloro-*cis*-5a,6,7,8,9,9a-hexahydrodibenzofuran-4-carboxylate

2-Chloro-*cis*-5a,6,7,8,9,9a-hexahydrodibenzofuran-4-carboxylic acid (EP-A-0339950), (0.100g, 0.396 mmol) was suspended in thionyl chloride (5 ml) and heated to reflux with stirring. After 1h, the reaction mixture was allowed to cool, and was evaporated under reduced pressure to give a pale brown oil, which was dried *in vacuo* in give the crude acid chloride. Meanwhile a solution of 1-butyl-4-piperidinylmethanol (0.075g, 0.436 mmol) in dry THF (3 ml) under argon was treated with 1.6M n-butyllithium (0.272 ml, 0.436 mmol). After 0.25h, a solution of the crude acid chloride in dry THF (5 ml) was added, and the resultant mixture stirred at room temperature overnight. The reaction mixture was then evaporated under reduced pressure and purified by silica-gel chromatography (2% $MeOH/CH_2Cl_2$ as eluant) to give the ***title compound*** (0.071g, 44%) as a colourless oil, which was converted to its oxalate salt.

m.pt 154-155° C

^1H NMR (250 MHz, $CDCl_3$) (free base) δ :

7.70 (d, 1H), 7.20 (d, 1H), 4.85 (m, 1H), 4.18 (d, 2H), 3.25 (m, 1H), 3.05 (d, 2H), 2.43 (t, 2H), 2.13-1.70 (m, 8H), 1.65-1.25 (m, 11H), 0.95 (t, 3H).

Example 4-3 [R_1 = H, R_2 = Cl, R_3 = H, R_4 = H, X = O, A is a single bond, f, g, together are a bond, Y = O, Z = (i)]

(1-Butyl-4-piperidinylmethyl)-2-Chloro-6,7,8,9-tetrahydrodibenzofuran-4-carboxylate

The ***title compound*** was prepared from 2-chloro-6,7,8,9-tetrahydrodibenzofuran-4-carboxylic acid (EP-A-0339950) according to the methodology described in Example 3-3 and was converted to its oxalate salt.

m.pt 188-190° C

^{1}H NMR (200 MHz, $CDCl_3$) (free base) δ :
7.78 (d, 1H), 7.53 (d, 1H), 4.28 (d, 2H), 3.03 (d, 2H), 2.80 (t, 2H), 2.58 (t, 2H), 2.10-1.75 (m, 9H), 1.52-1.25 (m, 6H), 0.90 (t, 3H).

Example 1-4 [X = O, R_1 = H, R_2 = Cl, R_3, R_4', R_4'' = H, Y = O, Z = (i)]
10-(1-Butylpiperidin-4-ylmethyl)-8-chloro-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxacinecarboxylate

The title compound is prepared from 8-chloro-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxacin-10-carboxylic acid (R.D. Youssefyeh et al., J.Med.Chem. 1992, 35, 903) and lithium (1-butylpiperidin-4-yl) methoxide *via* the imidazolide.

5-HT_4 RECEPTOR ANTAGONIST ACTIVITY

1) Guinea pig colon

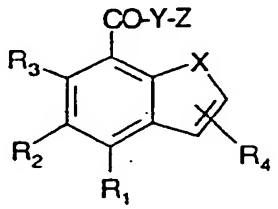
Male guinea-pigs, weighing 250-400g are used. Longitudinal muscle-myenteric plexus preparations, approximately 3cm long, are obtained from the distal colon region. These are suspended under a 0.5g load in isolated tissue baths containing Krebs solution bubbled with 5% CO_2 in O_2 and maintained at 37°C. In all experiments, the Krebs solution also contains methiothepin 10^{-7}M and granisetron 10^{-6}M to block effects at 5-HT_1, 5-HT_2 and 5-HT_3 receptors.

After construction of a simple concentration-response curve with 5-HT, using 30s contact times and a 15min dosing cycle, a concentration of 5-HT is selected so as to obtain a contraction of the muscle approximately 40-70% maximum(10^{-9}M approx). The tissue is then alternately dosed every 15min with this concentration of 5-HT and then with an approximately equi-effective concentration of the nicotine receptor stimulant, dimethylphenylpiperazinium (DMPP). After obtaining consistent responses to both 5-HT and DMPP, increasing concentrations of a putative 5-HT_4 receptor antagonist are then added to the bathing solution. The effects of this compound are then determined as a percentage reduction of the contractions evoked by 5-HT or by DMPP. From this data, pIC_{50} values are determined, being defined as the -log concentration of antagonist which reduces the contraction by 50%. A compound which reduces the response to 5-HT but not to DMPP is believed to act as a 5-HT_4 receptor antagonist.

The compounds generally had a pIC_{50} of at least 7.

Claims

1. Compounds of formula (I), wherein formula (I) consists of formulae (I-1) to (I-4), and pharmaceutically acceptable salts thereof, and the use of a compound of formula (I) or a pharmaceutically acceptable salt thereof:



(I-1)

wherein

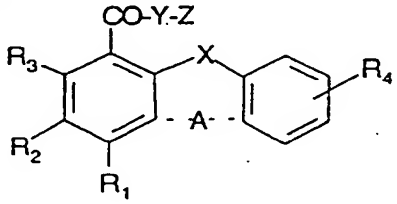
X is O or S;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;

R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

R_4 is hydrogen or C_{1-6} alkyl;



(I-2)

wherein

X is O or S;

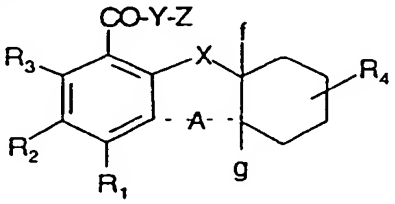
A represents a single bond, $-CH_2-$, or CO or A is $(CH_2)_a$-E-$(CH_2)_b$ where one of a and b is 0 and the other is 0 or 1 and E is O, S or NH;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;

R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

R_4 is hydrogen or C_{1-6} alkyl;



(I-3)

wherein

X is O or S;

A represents a single bond, $-CH_2-$, or CO or A is $(CH_2)_a$-E-$(CH_2)_b$ where one of a and b is 0 and the other is 0 or 1 and E is O, S or NH;

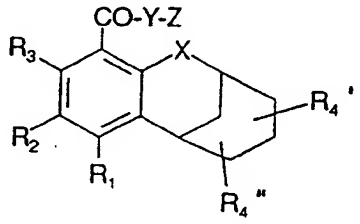
f and g are both hydrogen or together are a bond;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;

R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

R_4 is hydrogen or C_{1-6} alkyl;



(I-4)

wherein

X is O or S;

R_1 is hydrogen, amino, halo, C_{1-6} alkyl, hydroxy or C_{1-6} alkoxy;

R_2 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy, nitro, amino or C_{1-6} alkylthio;

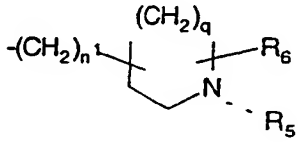
R_3 is hydrogen, halo, C_{1-6} alkyl, C_{1-6} alkoxy or amino;

R_4' and R_4'' are independently hydrogen or C_{1-6} alkyl;

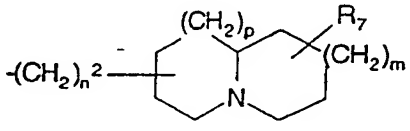
In formulae (I-1) to (I-4) inclusive:

Y is O or NH;

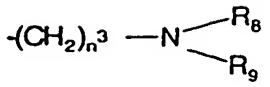
Z is of sub-formula (a), (b) or (c):



(a)



(b)



(c)

wherein

n^1 is 0, 1, 2, 3 or 4; n^2 is 0, 1, 2, 3 or 4; n^3 is 2, 3, 4 or 5;

q is 0, 1, 2 or 3; p is 0, 1 or 2; m is 0, 1 or 2;

R_5 is hydrogen, C_{1-12} alkyl, aralkyl or R_5 is $(CH_2)_z$-R_{10} wherein z is 2 or 3 and R_{10} is selected from cyano, hydroxyl, C_{1-6} alkoxy, phenoxy, $C(O)C_{1-6}$ alkyl, COC_6H_5, $-CONR_{11}R_{12}$, $NR_{11}COR_{12}$, $SO_2NR_{11}R_{12}$ or $NR_{11}SO_2R_{12}$ wherein R_{11} and R_{12} are hydrogen or C_{1-6} alkyl; and

R_6, R_7 and R_8 are independently hydrogen or C_{1-6} alkyl; and

R_9 is hydrogen or C_{1-10} alkyl;

or a compound of formula (I) wherein the CO-Y linkage is replaced by a heterocyclic bioisostere;

in the manufacture of a medicament having 5-HT_4 receptor antagonist activity.

2. A compound according to claim 1 wherein:

In formula (I-1):

R_1 is hydrogen or amino, R_2 is hydrogen or halo, R_3 is hydrogen or halo, R_4 is hydrogen;

In formula (I-2):

R_1 is hydrogen or amino, R_2 is hydrogen or halo, R_3 is hydrogen or halo, R_4 is often hydrogen;

In formula (I-3):

R_1 is hydrogen or amino, R_2 is hydrogen or halo, R_3 is hydrogen or halo, R_4 is hydrogen;

In formula (I-4):

R_1 is hydrogen or amino, R_2 is hydrogen or halo, R_3 is hydrogen or halo, R_4' and R_4'' are hydrogen.

3. A compound according to claim 1 or 2 wherein the moiety attached to CO-Y-Z is that which is as contained in any of the Examples described herein.

4. A compound according to any one of claims 1 to 3 wherein Z is of sub-formula (a) and $(CH_2)_{n1}$ is attached at a carbon atom of the azacycle.

5. A compound according to claim 4 wherein Z is N-substituted 4-piperidylmethyl.

6. A compound according to claim 5 wherein the N-substituent is C_2 or greater alkyl, or optionally substituted benzyl.

7. (1-Butyl-4-piperidinylmethyl)-4-amino-5-chlorobenzo[b]furan-7-carboxamide,
(1-butyl-4-piperidinylmethyl)benzothiophene-7-carboxylate,
(1-butyl-4-piperidinylmethyl)-5-chlorobenzo[b]furan-7-carboxylate, or
(1-butyl-4-piperidinylmethyl)-5-chlorobenzo[b]furan-7-carboxamide.

8. 1-Butylpiperidin-4-ylmethyldibenzofuran-4-carboxylate,
(1-butyl-4-piperidinylmethyl)-9H-xanthene-4-carboxylate,
(1-butyl-4-piperidinylmethyl)-9-oxo-9H-xanthene-4-carboxylate,
(1-butyl-4-piperidinylmethyl)-10H-phenoxazine-4-carboxylate,
(1-butyl-4-piperidinylmethyl)-1-amino-2-chlorodibenzofuran-4-carboxamide,
(1-butyl-4-piperidinylmethyl)-1-amino-2-chlorodibenzofuran-4-carboxylate, or
(1-butyl-4-piperidinylmethyl)-2-chlorodibenzofuran-4-carboxylate.

9. (1-Butyl-4-piperidinylmethyl)-1-amino-2-chloro-5a,6,7,8,9,9a-tetrahydrodibenzofuran-4-carboxylate,
(1-butyl-4-piperidinylmethyl)-1-amino-2-chloro-5a,6,7,8,9,9a-tetrahydrodibenzofuran-4-carboxamide,
(1-butyl-4-piperidinylmethyl)-2-chloro-*cis*-5a,6,7,8,9,9a-hexahydrodibenzofuran-4-carboxylate, or
(1-butyl-4-piperidinylmethyl)-2-chloro-6,7,8,9-tetrahydrodibenzofuran-4-carboxylate.

10. 10-(1-Butylpiperidin-4-ylmethyl)-8-chloro-3,4,5,6-tetrahydro-2,6-methano-2H-1-benzoxacinecarboxylate.

11. A compound according to any one of claims 7 to 10 in the form of a pharmaceutically acceptable salt.

12. A compound according to any one of claims 7 to 10 but wherein Y is NH.

13. A process for preparing the ester or amide compounds (where Y is O or NH) according to claim 1, which comprises reacting an appropriate acid derivative with an appropriate alcohol or amine.

14. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12, and a pharmaceutically acceptable carrier.

15. A compound according to claim 1 for use as an active therapeutic substance.

16. The use of a compound according to claim 1 in the manufacture of a medicament for use as a 5-HT_4 receptor antagonist.

17. The use according to claim 16 for use as a 5-HT_4 receptor antagonist in the treatment or prophylaxis of gastrointestinal disorders, cardiovascular disorders and CNS disorders.

INTERNATIONAL SEARCH REPORT

Ir [redacted] Application No
PCT/EP 93/02809

A. CLASSIFICATION OF SUBJECT MATTER
IPC 5 C07D405/12 C07D409/12 C07D413/12 C07D307/79 C07D333/54
C07D311/78 A61K31/38 A61K31/35 A61K31/34 A61K31/445

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 5 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP-A-0 270 342 (TANABE SEIYAKU CO., LTD.) 8 June 1988 see page 2, line 30 - line 38; claims ---	1,2,4-7, 11-17
X	EP-A-0 496 064 (FARMITALIA CARLO ERBA S.R.L.) 29 July 1992 see the abstract; claims; page 11, lines 3 - 6 ---	1,2,4-7, 11-17
D,X A	EP-A-0 234 872 (ADRIA LABORATORIES INC.) 2 September 1987 see the whole document --- -/--	1,2,4-6, 11-17 7

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 January 1994	30. 03. 94
Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax (+ 31-70) 340-3016	Authorized officer Paisdor, B

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
D,X A	EP-A-0 493 041 (ERBAMONT, INC.) 1 July 1992 see the abstract; page 3, line 1 - page 5, line 36; claims	1,2,4-6, 11-17 7
A	EP-A-0 407 137 (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 9 January 1991 see page 9, line 17 - line 26; claims	1,2,4-7, 11-17
A	EP-A-0 445 862 (JANSSEN PHARMACEUTICA N.V.) 11 September 1991 see the whole document	1,2,4-7, 11-17
D,A	EP-A-0 501 322 (GLAXO GROUP LIMITED) 2 September 1992 see page 5, line 18 - line 43; claims 1,15	1,2,4-7, 11-17
P,A	WO-A-93 16072 (SMITHKLINE BEECHAM P.L.C.) 19 August 1993 see the whole document	1,2,4-7, 11-17
P,D, A	WO-A-93 05038 (SMITHKLINE BEECHAM P.L.C.) 18 March 1993 see the whole document	1,2,4-7, 11-17
P,D, A	WO-A-93 02677 (SMITHKLINE BEECHAM P.L.C.) 18 February 1993 see the whole document	1

INTERNATIONAL SEARCH REPORT

[redacted]ional application No.
PCT/EP 93/02809

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.: 3 (not searched) 1,2, 4-6, 11-17 (searched incompletely)
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
Claim 3 does not meet the requirements of Art. 6 and Rule 6.2(a) PGT, because the wording of claim 1 "... wherein the CO-Y linkage is replaced by a heterocyclic bioisostere" is not clear and concise, and also encompasses such an enormous number of possible compounds that a complete search is not possible on economic grounds

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
1. Claims 7, 1, 2, 4-6, and 11-17 partially and only insofar as compounds of forumula (I-1) of cl. 1 are concerned
2. Claims 8, 1, 2, 4-6 and 11-17 concerning compounds of formula (I-2) of cl. 1
3. Claims 9, 1, 2, 4-6 and 11-17 concerning compounds of formula (I-3) of cl. 1
4. Claims 10, 1, 4-6 and 11-17 concerning compounds of formula (I-4) of cl. 1

.For further information please see Form PCT/ISA/206 dated 10.02.1994

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searches without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: mentioned in the first invention.

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP[redacted]/02809

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A-0270342	08-06-88	JP-A-	63139180	10-06-88
		FR-A-	2608605	24-06-88
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		CA-A-	2099107	28-06-92
		WO-A-	9212147	23-07-92
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		AU-A-	1209492	15-09-92
		WO-A-	9214727	03-09-92
WO-A-9316072	19-08-93	AU-A-	2541892	05-04-93
		AU-B-	3457293	03-09-93
		CN-A-	1073173	16-06-93
		WO-A-	9305038	18-03-93

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 93/02809

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AU-A-	2541892	05-04-93
		WO-A-	9305040	18-03-93
		PT-A-	100854	29-10-93
		PT-A-	100855	30-11-93
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		CN-A-	1073173	16-06-93
		AU-B-	3457293	03-09-93
		WO-A-	9316072	19-08-93
		AU-B-	4081393	30-12-93
		WO-A-	9324117	09-12-93
		WO-A-	9400113	06-01-94
WO-A-9302677	18-02-93	AU-A-	2363492	02-03-93